Factors that Impact Opioid Agonist Therapy in Northern and Rural Ontario

by

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Abstract

Opioid agonist therapy is the gold standard of care for opioid dependence. However, the efficacy of treatment may be hindered by concurrent drug use, including cocaine and benzodiazepines. This thesis examines the impact of concurrent drug use on treatment retention, and whether it is differentially impacted by geographic region. We conducted a retrospective cohort study using electronic medical records from 58 opioid agonist therapy clinics in Ontario. One-year treatment retention was the primary outcome of interest. Both baseline cocaine and benzodiazepine users experienced decreased retention rates than non-users. Patients who used concurrent drugs at higher frequencies experienced decreased retention rates compared to those who used less often. Northern and urban patients were more likely to be baseline cocaine users, and Southern urban patients were more likely to be benzodiazepine users. Both baseline and continued concurrent drug use is predictive of treatment drop out in Northern and Southern patients.

Keywords

Opioid agonist therapy, treatment retention, methadone, buprenorphine, rurality, Northern Ontario, concurrent drug use, cocaine, benzodiazepines

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Chapter 1- Geography and Substance Use: Evaluating Factors That Impact Opioid Agonist Therapy in the North

Opioids are among the most frequently prescribed medications in Canada, and prescribing rates continue to rise (Dhalla et al. 2009). Along with the increase in the prescribing of opioids, the pattern of opioid use disorders has recently undergone a change; heroin use has decreased, and the misuse of prescribed opioids has increased (Fischer et al. 2006). The rate of oxycodone prescribing increased by an alarming 850% between the years of 1991 and 2007 (Dhalla et al. 2009). In Ontario, the number of opioid-related deaths has increased dramatically in recent decades. Between the years of 1991 and 2010, the rate of opioid-related deaths increased by 242%, with an average age of mortality only 42 years of age (Gomes et al. 2014). In one population-based study of drug-related deaths in Ontario, nearly 60% were attributed to opioids, with oxycodone accounting for a third of all opioid-related deaths (Madadi et al. 2013).

The prescription opioid abuse crisis in Northern Ontario communities, including First Nations, rural, and remote communities, is especially dire (Kiepek et al. 2012). First Nation peoples are an estimated two to five times more likely to die due to overdose than the general population (Milloy et al. 2010). In a study of opioid prescribing and opioid-related death in Ontario, Northern communities experience some of the highest rates (Gomes et al. 2011). Over a three year time period from January 2004 to December 2006, the Thunder Bay District displayed the highest rate of opioid prescribing (12,635 opioid prescriptions dispensed per 1,000 Ontario Public Drug Program eligible) and the second highest rate of opioid-related death (9.3 per 100,000 per year), following Manitoulin District (11.9 per 100,000 per year). The Municipality of Sudbury ranked in the top 10

for both measures.

In this thesis, we discuss methadone and buprenorphine for the treatment of opioid-dependence and evaluate the factors affecting treatment retention for those patients living in Northern, rural, and remote areas living with opioid dependence – including geography and concurrent drug use.

Methadone and Buprenorphine

Methadone and buprenorphine are long-acting opioids available for the treatment of opioid dependence; this treatment strategy is known as opioid agonist therapy (OAT). OAT is a substitution therapy with the goal of harm reduction and improved psychosocial functioning (CPSO, 2011). OAT benefits the patient by relieving opioid withdrawal and stabilizing psychological, physical, and social functioning (CPSO, 2011), and has been shown to reduce mortality rates among opioid dependent populations (Soyka et al. 2011)

Methadone maintenance therapy (MMT) is considered to be the standard of care for patients with opioid-dependence (CPSO, 2011). Methadone is a full opioid receptor agonist that is administered orally in liquid form. Methadone dosing is typically observed by a pharmacist, nurse, or by a physician to discourage the diversion of the medication. By federal regulation, dosing must be witnessed by a regulated health professional. MMT not only reduces illicit heroin use, but also reduces the use of other substances – including cocaine, amphetamines, and sedatives (Mattick et al. 2014). Studies have also found that patients who receive high-dose methadone are less likely to use illicit opiods and more likely to be retained in treatment than those patients receiving low-dose methadone (Johnson et al. 2000). Another form of OAT is the combination sublingual tablet form of buprenorphine and naloxone, which – in Canada – is available as both

generic form and under the brand name Suboxone®. Buprenorphine is a partial agonist that acts to relieve the patient of their withdrawal symptoms. While having lower maximum effect than methadone, the effects of buprenorphine are longer lasting (Mattick et al. 2014). Compared to methadone, buprenorphine poses a much lower risk of overdose due to it being a partial opioid receptor agonist and being formulated with naloxone, an opioid receptor antagonist. However, studies have shown that patients who are taking buprenorphine are more likely to continue the use of illicit opioids (Mattick et al. 2014) and are at higher risk of dropping out of care (Fischer et al. 1999; Bell et al. 2006), potentially due to slow induction (Petitjean et al. 2001).

In Ontario, the availability of OAT has expanded substantially over the past two decades. The number of patients initiating OAT in Ontario rose from 6,000 to over 30,000 between the years of 2000 and 2010 (CAMH, 2011). Currently, there are over 42,000 patients receiving OAT in the Province of Ontario (CPSO, 2015). With over 50 clinics across Ontario, the largest network of OAT clinics is the Ontario Addiction Treatment Centres (OATC). These clinics are distributed across the province and are operated under common management. Although the majority of clinics are concentrated in Southern Ontario, there remains a good representation of clinics in Northern areas. However, many areas of the province – particularly Northern and rural areas of Ontario – are still facing barriers in accessing treatment for opioid dependence. The data presented in this thesis is derived from anonymized electronic health records from the OATC clinic network between January of 2011 and June of 2013.

Impact of Northern and Rural Geography on OAT

Due to the strict requirement for physician approval (recommendation from the provincial licensing body leading to an exemption from the federal narcotics law), methadone is often unavailable in rural and remote communities (Kiepek et al. 2012). Compared to methadone, buprenorphine has fewer prescribing limitations and prescribing physicians do not require special approval (CPSO, 2011). Aside from a lack of physicians, people living in rural and remote communities often face additional barriers to health care, including having to travel long distances to access pharmacies (Kiepek et al. 2012). In a retrospective cohort study on patients initiating MMT in Ontario, more than half of patients living in Northern rural areas resided more than 125 km from their addiction treatment provider. This was compared to only 16 km for those residing in Southern urban communities (Eibl et al. 2015).

Despite the greater challenges in receiving health care services, it may be the case that patients seeking MMT in Northern communities have better treatment outcomes (Eibl et al. 2015). In a retrospective cohort study of 48 addiction treatment clinics in Ontario, the duration of time that patients were retained in treatment was significantly influenced by geographic location; patients residing in Southern urban communities remained in treatment for a shorter period of time, while those in Northern rural regions experienced enhanced treatment retention (Eibl et al. 2015). Theories as to why this pattern exists include: that there is less availability of illicit drugs in these areas, or that the patients who overcome the geographic barriers and do access OAT are inherently more motivated to be successful in treatment. Both of these theories are further explored later in this thesis.

Due to the numerous barriers that Northern, rural, and remote communities are faced with, patients often rely on alternate forms of health care, including telemedicine. Telemedicine – or telehealth – mitigates the barrier that rural and remote communities face when accessing medical care. In a retrospective cohort study of OAT clinics in Ontario, telemedicine was the primary treatment modality for all clinics that were considered Northern rural (Eibl et al. 2016). In a study of over 7,000 patients initiating OAT in Ontario, 3,618 patients had received more than 75% of their care via telemedicine (Eibl et al. 2016). Of note, these patients experienced retention rates that were equal to those patients primarily receiving in-person care (Eibl et al. 2016). Despite facing several barriers when accessing health care, patients receiving OAT in Northern rural areas appear to benefit from telemedicine, which mitigates the geographic isolation often experienced by people who live in these remote communities.

Benzodiazepines and OAT

While OAT has proven a very cost-effective form of treatment, the course of OAT may be negatively impacted by concurrent drug use, such as the use of benzodiazepines (BZDs) (Brands et al. 2008; Schiff et al. 2007). BZDs are a class of psychoactive drugs that are non-opioid central nervous system depressants. The short-term use of BZDs is clinically indicated for the treatment of anxiety, acute seizures, and acute alcohol withdrawal (Brands et al. 2000). There is currently a lack of evidence for the long-term use of BZD (Nielsen et al. 2015). Despite the fact that patients who use BZDs during OAT are at increased risk of overdose and death (Brands et al. 2008), BZD use in OAT is not uncommon (Bleich et al. 2002; Backmund et al. 2005; Bramness et al. 2007) with as many as 37% (Drake et al. 1993) to 66% (Iguchi et al. 1993; Nielsen et al. 2007) of

patients in MMT self-reporting concurrent BZD use. In a cross-sectional study of 170 patients who were receiving OAT, 24.1% met the criteria for BZD dependence, according to the Diagnostic Statistical Manual of Mental Disorders-IV (DSM-IV) (Lavie et al. 2008).

Patients who are receiving OAT and use BZD concurrently are at increased risk of overdose and death. In a retrospective study of opioid-related deaths in Ontario, 59.5% involved BZDs (Dhalla et al. 2009). In a nested case-control study of over 43,000 Ontario patients receiving MMT, concurrent BZD use was independently associated with opioid-related death (Leece et al. 2015). Additionally, patients who had received a BZD prescription within the past year were twice as likely to suffer from an opioid-related death (Leece et al. 2015). Aside from being at greater risk of overdose and death, patients who are receiving OAT and use BZDs on an ongoing basis are more likely to continue polydrug use – including cocaine and other opioids (Brands et al. 2008). Some studies have even found that repeated BZD exposure may modify the metabolism of both methadone and buprenorphine (Linterzeris et al. 2006).

One of the markers for a positive treatment outcome in OAT is one-year treatment retention. Treatment retention has shown to be correlated with a variety of positive health outcomes for patients, including reduced rates of drug use, hospitalization, criminal activity, and mortality (Peles et al. 2008, Nosyk et al. 2010). While it is known that BZD use during treatment is correlated with a more complex clinical course (Brands et al. 2008; Schiff et al. 2007) and has been shown to impact various patient outcomes including unemployment, criminality, and psychological distress (Brands et al. 2008), the literature is quite mixed as to whether BZD use impacts one-year treatment retention.

Several studies have found that patients who use BZD are at increased risk of premature drop-out (Schiff et al. 2007; Peles et al. 2010; Specka et al. 2011), and others have found that they are not (Kellogg et al., 2006; Peles et al. 2006; Brands et al. 2008). Several of these studies were cross-sectional rather than retrospective or relied on patient self-report of BZD use rather than urine toxicology, and few have had a comparable sample size to ours. Aside from these factors, the impact of BZD use on patients receiving OAT in Northern rural Ontario has not been studied, and is one of the main novelties of this thesis.

One important caveat is the nature of BZD use, and whether it is prescribed or non-prescribed. The majority of studies that have examined BZD use in OAT have not distinguished between the two. Despite the fact that BZD use in OAT puts patients at increased risk of overdose and death, BZD are often prescribed to these patients (Park et al. 2015). A retrospective cohort study of over 2,000 patients receiving OAT found that 40% had received a BZD prescription (Bramness et al. 2007). This number is alarmingly high, compared to the 5% of the general age-matched population receiving BZD prescriptions (Bramness et al. 2007). However, more than 60% of prescribing was by a physician other than the OAT provider. Among the 40% who received a prescription, they were more likely to be receiving methadone than suboxone and were more likely to be female. When the source of BZD is considered, it appears that non-prescribed BZD use is correlated with decreased retention, but prescribed BZD use is not (White et al. 2014). In fact, the retention rates of those patients using prescribed BZD were nearly identical to those patients not using BZD at all. This was compared to those patients using non-prescribed BZD, who were more than six times likely to terminate treatment

prematurely (White et al. 2014). Therefore, the source of BZD and the nature of its use is important to consider when studying treatment retention. However, this is something that very few studies have done.

In terms of BZD prescribing by region, a retrospective cohort study revealed that patients are significantly more likely to have received a prescription for BZDs prior to treatment entry if they resided in a Northern rural community (Eibl et al. 2016). More research needs to be done to understand these prescribing patterns and whether prescribed BZD use impacts treatment retention differentially by geographic location.

Cocaine and OAT

Cocaine is another drug that is commonly used by patients in OAT. One group of researchers found that as many as 75% of patients enrolled in MMT experience concurrent cocaine use (Grella et al. 1995). This is of great concern given that research has shown that cocaine use is predictive of treatment dropout (DeMaria et al. 2000; Downey et al. 2000; Hartel et al. 1995; Magura et al. 2002; Brands et al. 2008). Not only are non-cocaine users retained in treatment at a higher rate, but these patients successfully complete treatment earlier than those patients with baseline cocaine use (Tzilos et al. 2009). Patients who use cocaine during MMT are also more likely to use heroin (Hartel et al. 1995), experience psychological disturbances (Grella et al. 1995), and have a higher risk profile for HIV (Grella et al. 1995). In a secondary analysis of 162 patients receiving buprenorphine treatment, both baseline and ongoing cocaine use were found to be predictive of poorer treatment outcomes, including opioid use and decreased retention rates (Sullivan et al. 2010).

Despite the impact of cocaine use on treatment retention being better understood, this has not been studied in a Northern rural Ontario context. In a retrospective cohort study of patients receiving OAT in Ontario, those that resided in a Northern community were more likely to have received a prescription for stimulants prior to treatment entry, compared to those patients residing in Southern Ontario (Eibl et al. 2015). Given the known complexities regarding concurrent drug use in OAT, it is important that research be done to understand the patterns of physician prescribing, especially when these substances may be negatively impacting treatment outcomes. Thus, we chose a postpositivist lens through which to interpret our results and a transtheoretical model through which knowledge translation may occur.

A Postpositivistic Approach

In studying the impact of BZD use and cocaine use on OAT retention, a postpositivistic approach was used to guide our thinking. Pospostivism is an amended version of positivism that is less dualistic. A key assumption of postpositivism is that evidence that is established through research is imperfect by nature (Creswell et al. 2009). This approach holds that our knowledge is shaped by data, evidence, as well as rational consideration and that research aims to produce findings that are both factual and of relevance in order to help researchers describe a relationship of interest – in this case, the relationship between concurrent drug use and treatment retention (Creswell et al. 2009). In doing so, we will try to remain as objective as possible and reflect on both our methods and our findings to identify any bias and to ensure that our conclusions are both valid and reliable.

The Transtheoretical Model

In applying a framework in a clinical context, the transtheoretical model may help physicians guide their patients along the stages of change. This model has been used previously in addiction research and focuses on what is needed for patients to alter their behavior to improve their health (Prochaska et al. 1992). The transtheoretical model describes five stages of readiness for change. The first stage is pre-contemplation, where the patient does not yet view their behavior as a threat to their health. The second stage is contemplation, where the patient is cognizant of their negative health behavior, and recognizes it as detrimental to their health. The third stage is preparation, where the patient now has intention of changing their behavior within the next month. The fourth stage is action, where the patient has made specific changes to improve their lifestyle, but these changes have been for six months or less. Lastly is the maintenance stage, where the patient has abstained from the negative health behaviour for at least six months (Prochaska et al. 1992). In our research, the negative health behavior refers to concurrent drug use, whether the use of BZD or cocaine while receiving OAT. The belief is that the extent to which a patient is ready for change may predict their likelihood of concurrent drug use, and therefore their likelihood of treatment retention. Despite patients in OAT being in the action stage with regards to their opioid use, they may be at an earlier stage with regards to their concurrent drug use. If this is the case, physicians should help tailor treatment to build motivation for patients to change their negative health behavior, whether it be the use of cocaine or BZD.

We will also be discussing the role of contingency management in OAT, which is one of the ten processes of change in the transtheoretical model. The concept behind

contingency management is that the physician provides a reward for positive behavior and punishment for negative behavior (Glanz et al. 2008). In OAT, take-home doses (known as carries) are often achieved as a result of contingency management, whereby abstaining from concurrent drug use will earn the patient carries (Brands et al. 2002). Overall, the transtheoretical model may help researchers better understand why patients use concurrent drugs and allow a better understanding of the steps that can be taken to increase patients' readiness for change and, therefore, increase treatment retention.

Hypothesis

Based on previous research, we expect that both baseline and ongoing BZD or cocaine use will negatively impact treatment retention, and that with an increasing prevalence of BZD or cocaine use, there will be a decrease in treatment retention. Furthermore, there will be differences in the extent to which concurrent drug use impacts OAT outcomes based on geographic location.

Summary

Currently, there exist several knowledge gaps with respect to addiction treatment in the North. Further research must be conducted to better understand the unique implications of opioid dependence in the North, such as: how Northern Ontario patients seeking OAT are impacted by their geographic location, what method of treatment delivery provides the most efficacious form of care, and how Northern Ontario patients receiving OAT are impacted by concurrent drug use in order to provide the highest quality of care to this unique and vulnerable population. Understanding nuances of the rural and remote geography of Northern Ontario may aid planners and policy makers to enhance care for patients living in these geographically isolated regions. In this thesis, we

explore how concurrent drug use uniquely impacts treatment retention for patients living in Northern and rural regions of the province, as well as make recommendations as to how we should proceed to enhance care for this patient population.

Chapter 2: The Impact of Cocaine Use on Treatment Retention

Opioids are a family of semi-synthetic molecules having a pharmacologically similar effect to morphine (derived from opium), a naturally existing pain reliever. Opioids are among some of the most commonly prescribed medications in Canada, and prescribing rates continue to rise (Dhalla et al. 2009). Opioids have a high incidence of dependence, with approximately 200,000 Canadians dependent on prescription opioids (Webster et al. 2012). Specifically in Ontario, prescription opioid related deaths increased by 242% between the years of 1991 and 2010 (Gomes et al. 2014).

For those who become opioid dependent, there is a treatment known as opioid agonist therapy (OAT), a maintenance therapy whereby the patient is relieved of their opioid withdrawal by taking either methadone or buprenorphine, and is able to return to normal social, psychological, and physical functioning. Patients in OAT experience better treatment outcomes when they are retained in treatment for at least one year, and there is considerable evidence to support that one year retention is strongly correlated with a variety of positive health outcomes including: reduced rates of drug use, relapse, hospitalization, mortality, and illegal activity (Peles et al. 2008; Nosyk et al. 2010). There are currently over 42,000 patients receiving OAT in Ontario (CPSO, 2015).

In remote communities, such as those in Northern Ontario, the opioid crisis is particularly rampant (Kiepek et al. 2012). These Northern communities experience some of the highest rates of opioid prescribing and opioid related death in the province (Gomes et al. 2011). Due to the vast geography of the North, these communities often face barriers when accessing various forms of health care, often relying on technology such as telemedicine to receive treatment (Eibl et al. 2016). Given the additional barriers that

Northern patients face, it is of great importance that OAT outcomes and factors relating to its success and failure be studied in this geographic context, to better understand how treatment can be tailored for these patients.

Although OAT has been shown to be a very cost effective form of treatment, its efficacy may be negatively impacted by concurrent drug use, including the use of cocaine. Cocaine is a stimulant that alters the brain's ability to regulate dopamine. By inhibiting dopamine reuptake, cocaine causes a dopamine accumulation at the synapse (NIDA, 2010). This increase in dopamine is typically associated with a temporary increase in energy, alertness, and mood (Boys et al. 2001). While cocaine use has been shown to increase cognitive function immediately after use, sustained long-term use appears to impair cognitive function (Spronk et al. 2013). Currently, there is no pharmacological treatment for cocaine dependence (Tzilos et al. 2009; Dutra et al. 2008), and current guidelines are limited to the use of cognitive behavioral therapy (CBT) and contingency management (Rawson et al. 2002; Epstein et al. 2003; Tzilos et al. 2009). However, research surrounding the efficacy of CBT and contingency management for cocaine dependence in OAT is inconclusive (Tzilos et al. 2009; Penberthy et al. 2010; Darker et al. 2012).

Studies have found that cocaine use is quite common in patients in OAT, with as many as 30-50% of patients self-reporting cocaine use at treatment initiation (Raffa et al. 2007; Cone et al. 2012; Roux et al. 2016). The prevalence of cocaine use in OAT is of great concern given that studies have found regular cocaine use to be predictive of poorer treatment outcomes. Specifically, cocaine-using patients tend to suffer from psychological distress (Roux et al. 2016), require higher doses of methadone to stabilize

(Maremanni et al. 2000), have a higher risk profile for HIV (Grella et al. 1995), are more likely to use heroin (Hartel et al. 1995), and are at increased risk of treatment drop-out (Brands et al. 2008; Salamina et al. 2010; Sullivan et al. 2010; Proctor et al. 2015). Additionally, a retrospective cohort study in the U.S. found that patients who regularly use cocaine while on OAT are at increased risk of overdose, with as many as one third of opioid related deaths involving cocaine (Visconti et al. 2015).

Given the greater clinical complexity of OAT patients who engage in cocaine use, it is of great importance to study this population in the context of Northern and rural settings, where patients are already faced with an abundance of barriers when accessing care. In this study, we investigate the impact of geography on cocaine use and treatment retention in Ontario, Canada.

Methods:

Clinical Context:

In Ontario, OAT is regulated by formal treatment guidelines established by the College and Physicians of Ontario (CPSO), which set out expectations with respect to physician practice and are enforced through peer-audits (CPSO 2011). These guidelines are in addition to the federal requirement for an exemption to prescribe methadone. Variability of practice within the guidelines is possible, but is generally limited. This study is based on the electronic medical records of patients treated within the Ontario Addiction Treatment Centres (OATC), a network of over 50 OAT clinics across the province operated under common management. Standardized evidence-based best practice policies and operating procedures are in place within the clinic network, which further limit the likelihood of variability of treatment between sites and between

physicians. To maintain consistency, patients are typically seen by the same physician throughout the course of their treatment.

Cohort Definition:

We conducted a retrospective cohort study of patients initiating OAT within OATC for the first time between January 1st, 2011 and June 17th, 2012 in the Province of Ontario. We defined first time OAT as no previous history of methadone or buprenorphine use in the OATC network, based on review of records dating back to 1999. Patients were started on either methadone or suboxone (the only two medications approved for this purpose in Canada at the time of the study) and were allowed to transition between these medications over the course of treatment. Patients were at least 15 years or older (patients < 18 years of age accounted for < 1% of cohort), and were residents of Ontario. All patients were followed from the date of OAT initiation to the date of medication discontinuation, or end of the study period (June 2013). Drug discontinuation was defined as a patient not receiving a dose of methadone or buprenorphine for 30 consecutive days.

Data Sources

The dataset used for this study was derived from anonymized electronic medical records from the OATC network of 58 addiction treatment centers across the Province of Ontario. Methadone prescribing, treatment delivery, and data management are harmonized across the clinic network. Prior to data analysis, personal identifiers were replaced with an encrypted unique identifier. Cluster analysis (testing relation between individual clinic and treatment retention) did not reveal any significant differences among

clinics with respect to increased/decreased treatment retention by individual clinic or physician.

Cocaine Use

Patients were categorized by baseline and ongoing cocaine use based on urine toxicology screening. Urine toxicology screening has the ability to detect benzoylecgonine – a metabolite of cocaine (Handford et al. 2011). Screening is performed on all patients one to two times per week throughout the treatment episode via an enzyme immunoassay, which has the ability to detect benzoylecgonine in the urine for 3 to 5 days (Handford et al. 2011). Patients were considered to be baseline cocaine users if they had any cocaine positive urine samples in their first month of treatment. Patients were also stratified into one of four groups depending on the frequency of cocaine positive urine samples throughout treatment.

Definition of Treatment Retention

Patients were followed from treatment initiation for at least one year, to a maximum follow-up date of June 17th, 2013. For the purpose of this study, treatment retention has been defined as being in treatment for one year of continuous and uninterrupted OAT, based on having received a prescription refill (for methadone or buprenorphine) within 30 days of the previous prescription end date (i.e. no period of 30 consecutive days without a dose of medication). One year treatment retention was chosen as the primary outcome of interest due to its correlation with positive health outcomes for patients (Peles et al. 2008; Nosyk et al. 2010).

In the event that a patient transitioned to a non-OATC clinic, was incarcerated, hospitalized, or was otherwise prevented from refilling their prescription for 30

consecutive days while still receiving treatment elsewhere, it is possible for type 1 error to occur (i.e. for the patient to be classified as having ended treatment despite continuing to be in care).

Statistical Analysis

Descriptive statistics were summarized for baseline characteristics of patients, and standardized differences were used to compare patient groups. Baseline characteristics included: percentage of patients that were male/female, Northern/Southern, and rural/urban, median age, median peak methadone dose, median days retained, the percentage of cocaine positive urine samples, and the one-year retention rate. For the purpose of this study, only a patient's first-treatment episode was considered. For the primary analysis, a Cox proportional hazard analysis was used to characterize the time to treatment discontinuation between the cocaine positive and negative patient groups with adjustment for the impact of age, gender, northern and rural location. Cox Proportional analysis and log-rank test were performed using SPSS 24.

Results:

Patient Demographics

Our cohort consisted of 3,835 patients across 58 clinics. The median age was 31.45 years and 59% of the cohort was male. 37% of the population resided in Northern Ontario (where 20 of the 58 clinics were located) and only 16% resided in a rural community. Patients residing in Northern Ontario were 41.2% less likely to drop out of treatment by the one-year mark, and males were 28.8% more likely to drop out than female patients. Transgendered patients were classified with their chosen gender identity group by the clinical team and therefore, a more nuanced analysis of gender is not

possible in this data set. There were no significant differences in treatment retention for patients living in rural or urban centres.

Baseline Cocaine Use

The cohort was stratified based on cocaine use at treatment initiation and throughout treatment. Of the 3,835 patients, 2,528 (65.9%) did not have cocaine positive urine samples in their first month of treatment, and 1,307 patients (34.1%) did. There were no gender differences (p=0.692) between the two groups, with both groups having approximately 59% male and 41% female patients. Patients were 49.5% less likely to have a cocaine positive urine sample in their first month of treatment if they lived in a rural area and were 24.3% more likely to have a cocaine positive urine sample in their first month of treatment if they lived in the North. First month cocaine users had an increased median peak dose of methadone (80 mg vs 75 mg), and had a lower median retention of 212 days, compared to 302 days.

Retention and Baseline Cocaine Use

Once patients were categorized by first month cocaine use, a Cox proportional analysis was performed to examine the proportion of patients retained in treatment for one year. The variables included in the analysis were: age [$_{a}$HR= 0.98 (95% CI 0.98 – 0.98)], gender (female [$_{a}$HR= 0.78 (95% CI 0.71 – 0.85)]), geography (North [$_{a}$HR= 0.59 (95% CI 0.53 – 0.65)] and rural [$_{a}$HR= 0.99 (95% CI 0.87 – 1.13)], and first-month cocaine use [$_{a}$HR= 1.12 (95% CI 1.03 – 1.23)]. Of those patients who did not have cocaine positive urine samples in their first month of treatment, 46% were retained at one year. This was compared to 39% for patients who were positive at baseline. Of non-users who were retained for one year, 89% were cocaine negative at one-year follow up. Of the

1,307 patients who had cocaine positive urines on admission, 508 remained in care at the one-year mark, 55% of which were cocaine negative. Lastly, patients were 12.4% more likely to not be retained in treatment if they had cocaine positive urine samples in their first month of treatment.

Proportion of Cocaine Positive Urine Samples

Patients were also categorized by the proportion of cocaine positive urine samples throughout treatment, separated into four groups (0-25%, 25-50%, 50-75% and 75-100% positive). Of the 3,835 patients, 2,941 had cocaine positive urine samples less than 25% of the time, and 48% of these patients were retained in treatment for one year. We found 333 patients had cocaine positive urine samples between 25-50% of the time – 37% of these patients were retained in treatment for one year. 207 patients had cocaine positive urine samples 50-75% of the time, and they experienced a retention rate of 33%**.** Compared to patients with < 25% of urines cocaine positive, these patients were 31.3% more likely to not be retained in treatment. 356 patients had cocaine positive urine samples more than 75% of the time, and they were retained at a rate of 22%. These patients were 96.5% more likely to not be retained, compared to the <25% group.

Cocaine Use and Geography

Patients were also stratified by location of residence. Patients were considered residents of Northern Ontario or Southern Ontario, as defined by the Local Health Integration Network (LHIN). If patients lived in LHIN 13 or 14, they were considered residents of Northern Ontario. For the four cocaine use groups listed above, the retention rates in the North were: 59%, 44%, 37%, and 31%, respectively. In Southern Ontario, retention rates were: 40%, 32%, 31%, and 19%, respectively. Despite having the same

frequency of cocaine positive urine samples, patients in Northern Ontario were 40.3% less likely to terminate treatment than were Southern patients.

Discussion:

Previous studies have concluded that cocaine use in OAT is predictive of a more complex clinical course, of poorer treatment outcomes, and lower retention rates (Raffa et al. 2007; Cone et al. 2012; Roux et al. 2016). Our results corroborate current findings in the literature that cocaine use is common among patients seeking OAT and that baseline cocaine use is predictive of decreased retention rates (Brands et al. 2008; Proctor et al. 2015). Given that cocaine use has been found to be predictive of treatment dropout, it is important to identify predictors of cocaine use in OAT. In our cohort, there were no significant differences in gender or age with respect to cocaine use. We did, however, find that geography was correlated with cocaine use. Patients who were from the North were more likely to use cocaine in their first month of treatment, as were patients living in urban areas. This may be due to the availability of cocaine, either in terms of cost of drug or its accessibility.

Studies have found that both baseline cocaine use and cocaine use throughout treatment are predictive of premature dropout (DeMaria et al. 2000; Downey et al. 2000; Hartel et al. 1995; Magura et al. 2002; Brands et al. 2008). In our study, patients who were not using cocaine at treatment initiation (those who had no cocaine positive urine samples during their first month of treatment) benefited from increased retention rates. Those patients who did have cocaine positive urine samples in their first month of treatment were 12.4% more likely to terminate treatment by the one-year mark than those

patients who were initially cocaine negative. This is not surprising given that cocaine use is a marker for greater clinical complexity, including premature dropout.

In this study, we examined one-year treatment retention for various frequencies of cocaine use. Patients were categorized by the percentage of cocaine positive urine samples throughout treatment duration: 0-25%, 25-50%, 50-75%, and 75-100%. We found that as frequency of cocaine use increases, the likelihood of treatment retention decreases. Roughly 48% of patients who had cocaine positive urine samples 0-25% of the time were retained in treatment for one full year and approximately 37% of patients who used 25-50% of the time were retained in treatment for one year. This number was lower for patients who had used 50-75% of the time (33%) and even lower for those patients who had used most often (22%). Patients who had 75% of more of their urines cocaine positive were nearly twice as likely to dropout of treatment. These findings support our hypothesis that cocaine use is correlated with treatment dropout, and that the more frequently a patients uses, the more likely they are to terminate treatment prematurely.

Once patients had been stratified by baseline cocaine use, they were also compared in terms of ongoing cocaine use throughout treatment. Of those patients who were negative on admission, 89% were cocaine negative at the 1-year mark. While this number is fairly high, this suggests that 11% of initial non-users either had a rate of cocaine use of less than once per month prior to OAT treatment entry or began using cocaine during treatment. Thus, it may be the case that patients have given up their opiate of choice, but have replaced it with another drug such as cocaine, but this is unusual. The vast majority of non-users remain non-users throughout the course of treatment. Of the patients who were cocaine positive on admission, more than half (55%) of those who

remained in treatment were cocaine negative at the 1-year mark. Given that OAT does not specifically treat cocaine dependence in a pharmacological sense, this may seem surprising. However, in both the Northern and Southern population, the percentage of patients with cocaine positive urine samples declined over the course of treatment for those patients who were retained. This is likely a result of contingency management whereby patients are motivated to abstain from cocaine use in order to obtain carried (i.e. take home) doses. Contingency management has been shown to reduce cocaine use in patients who are receiving methadone (Rawson et al. 2002). This decrease may also be a result of patients abstaining from illicit opioid use and making a change in lifestyle that reduced their contact with drug users or suppliers. Finally, there is some evidence from animal studies suggesting higher doses of methadone may reduce cocaine – as well as opioid – use (Leri et al., 2004).

In studying the impact of cocaine use on treatment retention, we focused on the relationship between cocaine use and retention in a Northern Ontario context. Due to the vast geographic landscape, Northern Ontario communities are often isolated from large urban centres. Because of this, these remote communities often face several barriers when accessing health care, especially when seeking OAT. A retrospective cohort study of patients seeking OAT in Northern Ontario found that more than half of patients residing in Northern rural communities lived 127 km or more from their addiction care provider, compared to only 16 km for their Southern urban counterparts (Eibl et al. 2015). Interestingly, this study also demonstrated that patients living in Northern areas were more likely to be retained in treatment than their Southern counterparts. While this may seem somewhat surprising given the barriers that Northern patients face, it may be that

these patients are more motivated to continue with treatment given the known difficulties in seeking OAT. Patients who have OAT at their disposal in Southern urban centers may not be as motivated to complete treatment, given that they could easily re-enter treatment if they dropout. It is clear from this study that the increased treatment retention in the North is not the result of lower prevalence of cocaine use in the North (in fact, Northern patients had a higher prevalence of cocaine use than Southern patients).

Until recently, it was thought that substance misuse was more prevalent in urban areas compared to rural (Lambert et al. 2008). However, studies have found that substance use is an issue of great relevance to people living in rural areas, with cocaine use being no exception. One study that relied on longitudinal survey information found that youth aged 12-17 living in rural areas experience increased rates of cocaine use compared to urban youth (Lambert et al. 2008). However, our results suggest that cocaine use is more common in the urban populations in Ontario. Our findings also indicate that patients who were cocaine negative on admission were more likely to live in a rural area, and were more likely to live in the South. These contrasting findings may be explained by differing types of data collection (self-reported cocaine use vs. urinalysis), different geographic contexts (Canada vs. US), or by different age distribution (youth vs. general population).

In using a postpositivistic approach, we have reflected on both our methods and our findings to identify any bias and limitations of our research. Firstly, if a patient terminated treatment, we were unable to determine the reason. It is possible that they simply terminated treatment, that they sought treatment through a non-OATC clinic, had an extended hospitalization or incarceration, or died. Secondly, due to the nature of a

retrospective cohort, we were unable to determine certain patient details, such as a patient's cocaine use history or the amount of cocaine used. Additionally, it is possible that the proportion of cocaine positive urine samples was misrepresented by patients who initiated treatment, dropped off one urine sample, then left treatment. Another limitation is that this study only focuses on one network of clinics offering OAT. The clinic network studied comprises approximately one third of the patients receiving OAT in Ontario. Therefore, there is the possibility of selection bias and that the findings within this clinic network may not generalize to other treatment settings in the Province. However, this can also be seen as a strength of the study, given that the standardized treatment in this clinic network adds integrity to the comparisons.

This study has many other strengths, one of which being the large sample size. With over 3,800 patients in the dataset, the study captures a considerable portion of patients receiving OAT in Ontario. The nature of data collection is another strength of this study. Previous studies looking at cocaine use by geographic region have been dependent on patient self-report, which is often unreliable. Although there is potential for error with urine toxicology, this method better captures true patterns of cocaine use amongst patients, particularly given the high frequency of urine testing in this sample (once to twice weekly). Lastly, while studies have been conducted on the impact of cocaine use in OAT, the remote Northern Ontario context has not been studied.

The findings of our study support the idea that cocaine use in OAT is predictive of poorer treatment outcomes, and that this is differentially affected by geographic region. Even with similar patterns of cocaine use, patients living in the North appear to benefit from greater retention rates. Knowing that cocaine use is a marker for greater

clinical complexity and decreased retention rates, it is important that physicians know the predictors of cocaine use and how to access specialized or enhanced treatment for the cocaine-using population.

Table 1. Characteristics of baseline cocaine users and non-users. Descriptive statistics were summarized for baseline characteristics of patients, and standardized differences were used to compare patient groups. Patients were considered baseline cocaine users if they had any cocaine positive urine samples in the first month of treatment

		Initially Negative (n = 2528, 65.9%)	**Initially Positive (n = 1307, 34.1%)**
Male / Female		1508 (59.7%) / 1020 (40.3%)	771 (59.0%) / 536 (41.0%)
North / South		906 (35.8%) / 1622 (64.2%)	496 (38.0%) / 810 (62.0%)
Urban / Rural		2076 (82.1%) / 452 (17.9%)	1163 (89.1%) / 143 (10.9%)
Median Age (Q_1, Q_3; SD)		31.7 (25.8, 40.8; SD=10.8)	30.7 (25.4, 39.1; SD=9.6)
Median Peak Methadone Dose (Q_1, Q_3; SD)		75 (50, 100; SD=34)	80 (60, 105; SD=33)
Median Peak Suboxone Dose (Q_1, Q_3; SD)		10 (8, 16; SD=7)	8 (8, 16; SD=7)
Median Days Retained (Q_1, Q_3; SD)		302 (53, 545; SD=277)	212 (62, 501; SD=260)
Median Percent Positive Results (Q_1, Q_3; SD)		0.0 (0.0, 1.3; SD=9.7)	34.4 (13.9, 76.7; SD=33.8)
Percent Positive Results	[0, 25)	2432 (96.2%)	507 (38.8%)
	[25, 50)	68 (2.7%)	265 (20.3%)
	[50, 75)	19 (0.8%)	188 (14.4%)
	[75, 100]	9 (0.4%)	347 (26.5%)
At Month 3 Day 60 to 90	Positive / Negative	207 (11.2%) / 1640 (88.8%)	635 (65.1%) / 340 (34.9%)
	Retained	1847 (73.1%)	975 (74.6%)
At Month 6 Day 150 to 180	Positive / Negative	218 (14.4%) / 1291 (85.6%)	444 (58.3%) / 317 (41.7%)
	Retained	1509 (59.7%)	716 (58.2%)
At Month 9 Day 240 to 270	Positive / Negative	164 (12.3%) / 1172 (87.7%)	315 (51.0%) / 303 (49.0%)
	Retained	1336 (52.8%)	618 (47.3%)
At Month 12 Day 330 to 360	Positive / Negative	135 (11.1%) / 1077 (88.9%)	246 (45.4%) / 296 (54.6%)
	Retained	1212 (47.9%)	542 (41.5%)
Retained / Not-Retained 365 Days		1163 (46.0%) / 1365 (54.0%)	508 (38.9%) / 799 (61.1%)

Figure 1.1 - Treatment retention by baseline cocaine use. A Cox proportional hazard analysis was used to characterize the time to treatment discontinuation between the patient groups. Log-rank comparison of these curves yielded a Chi-Square value of 8.975 with a significant p value of 0.0027. Baseline cocaine users were 12% more likely to drop out of treatment than baseline non-users [$_{a}$HR=1.124 (95% CI 1.03 –1.23)].

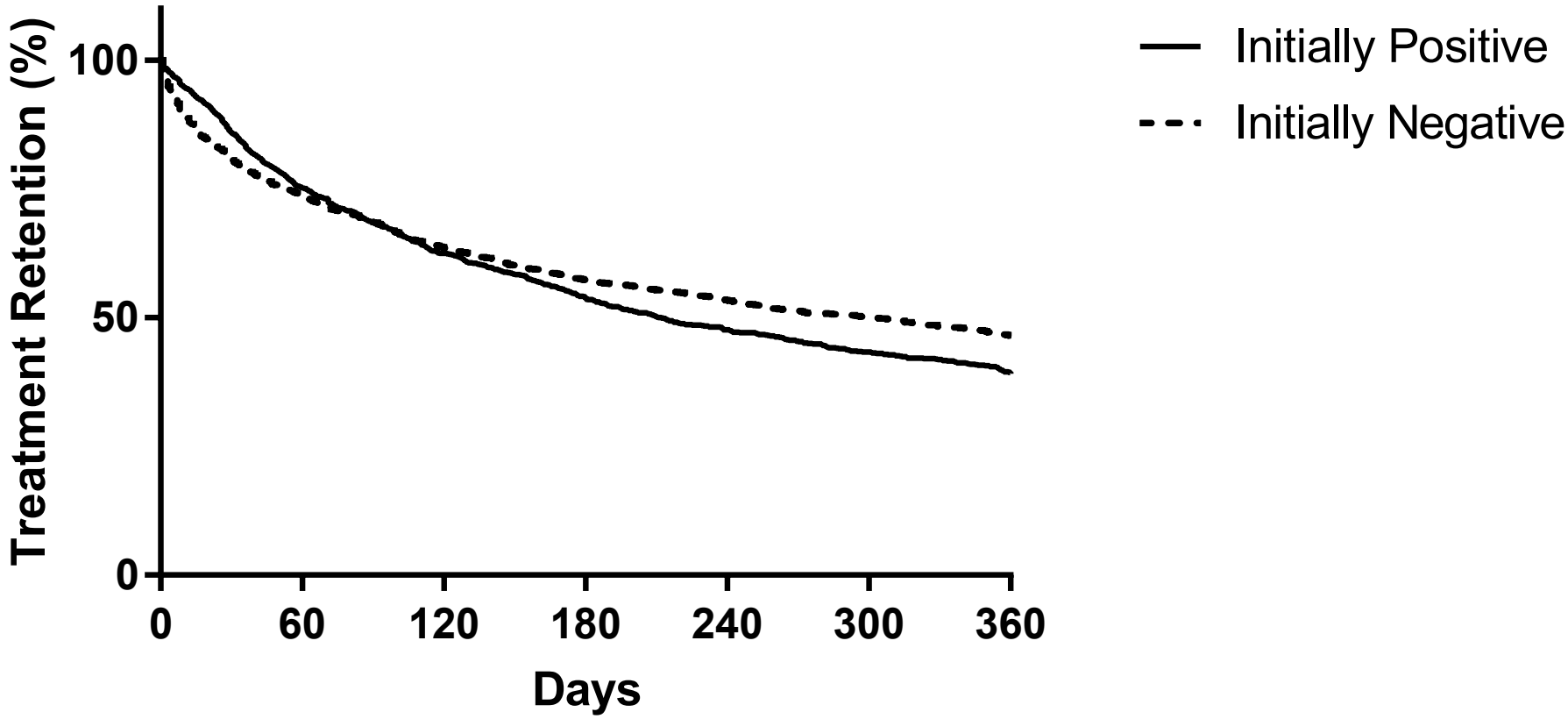


Figure 1.2 - Treatment retention by proportion of cocaine positive urine samples. A Cox proportional hazard analysis was used to characterize the time to treatment discontinuation across the four patient groups. Log-rank comparison of these curves yielded a Chi-Square value of 114.3 with a significant p-value of <0.0001. Patients with 50-75% of urines cocaine positive were 31% more likely to drop out of treatment than patients in the 0-25% reference group [$_{a}$HR=1.313 (95% CI 1.10 –1.56)]. Patients with 75-100% of urines cocaine positive were 96.5% more likely to drop out of treatment than patients in the 0-25% reference group [$_{a}$HR=1.97(95% CI 1.73 –2.24)].

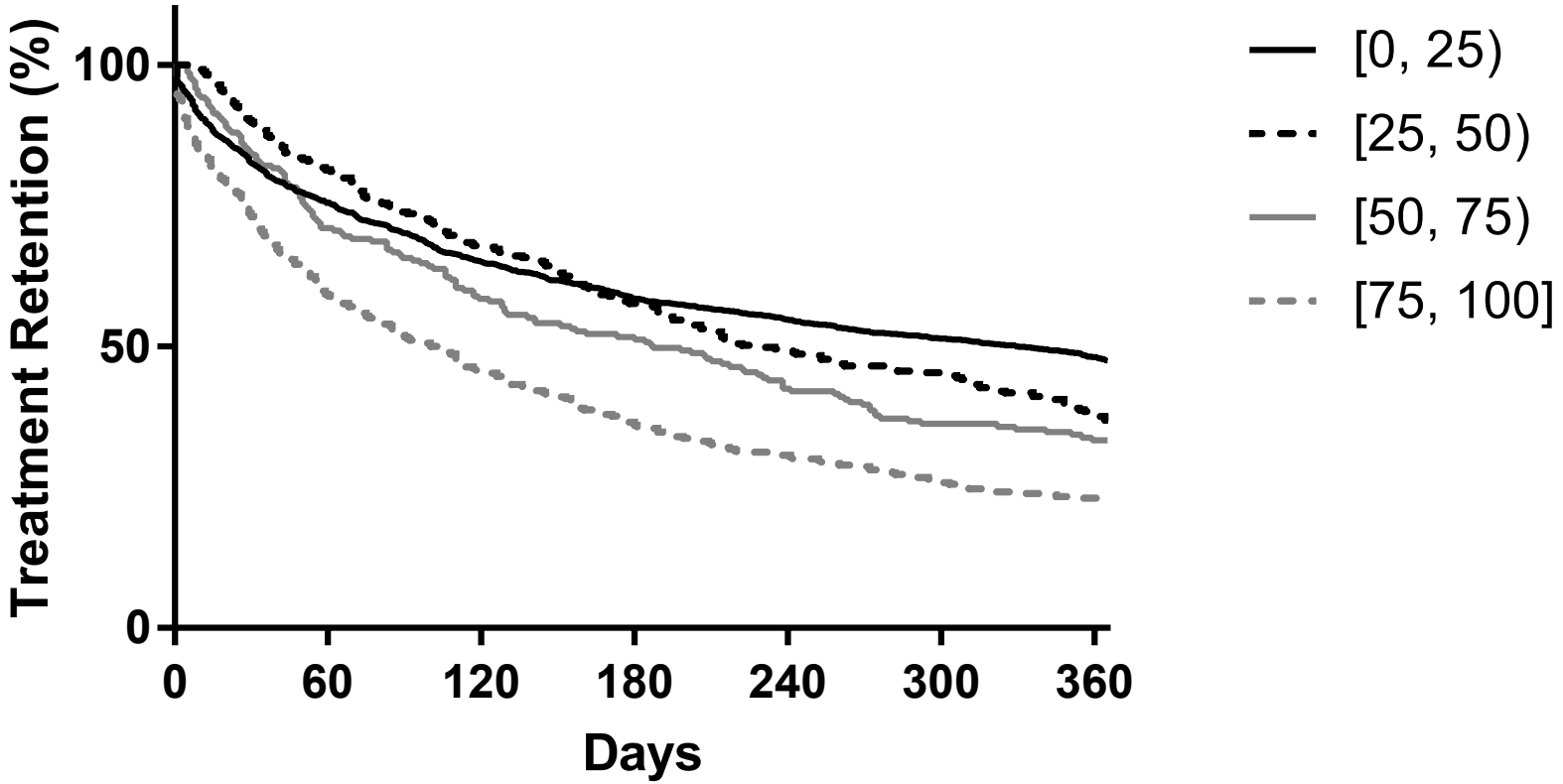
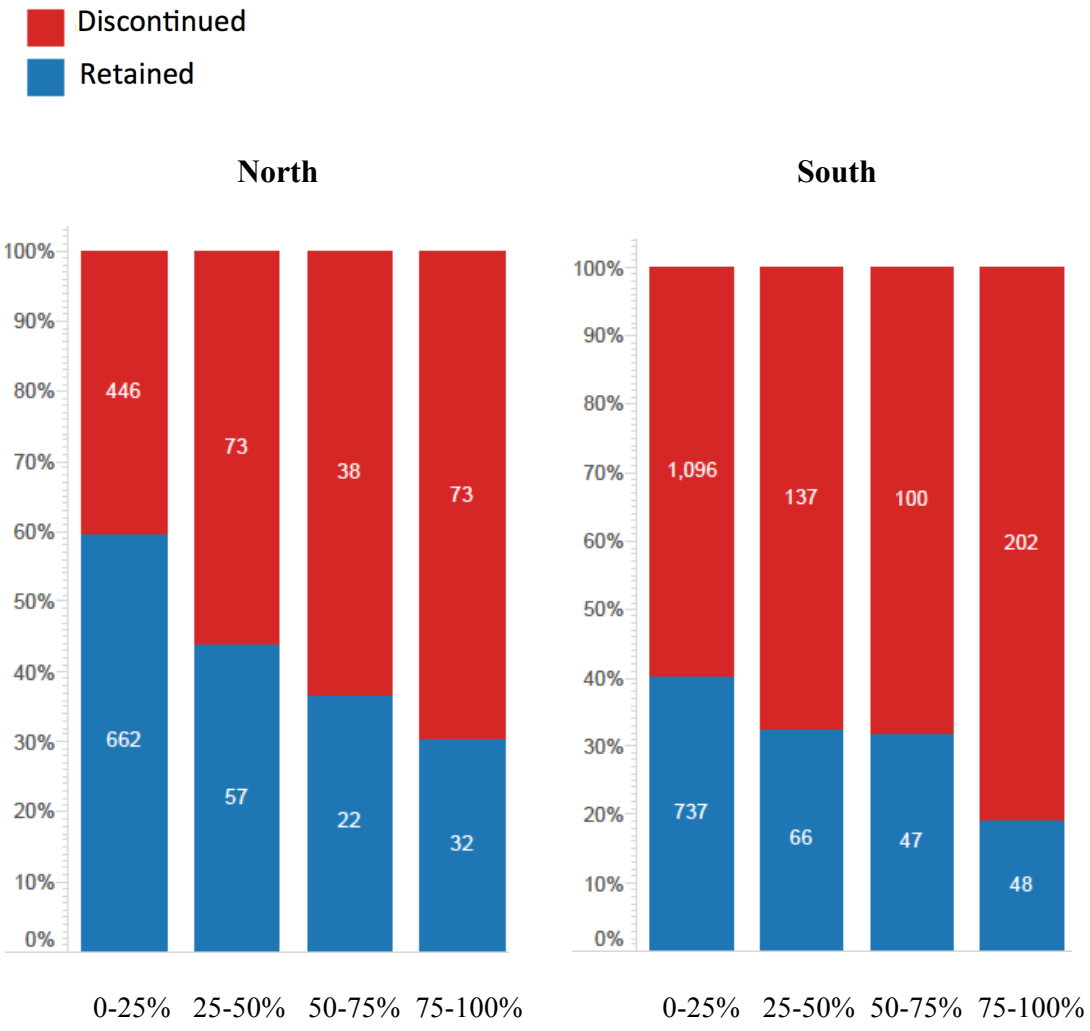


Figure 1.3 - Proportion of patients retained in treatment for one year, by frequency of cocaine use, comparing North vs. South. When considering similar proportions of cocaine positive urine samples, Northern patients benefit from increased retention rates compared to their Southern counterparts. Cross tabulations were performed. A significant association was found for the first (0-25%) group (Chi-Squared value = 105.7, p = 0.000), the second (25-50%) group (Chi-Square value = 4.37, p = 0.037), and the fourth (75-100%) group (Chi-Square value = 5.386, p = 0.02), but not with the third (50-75%) group (p=0.516).



Chapter 3: The Impact of Benzodiazepine Use on Treatment Retention

Opioids are one of the most frequently prescribed medications in Canada, and the misuse of prescription opioids is becoming increasingly more prevalent (Dhalla et al., 2009). In Ontario, the number of opioid-related deaths increased by an alarming 242% between 1991 and 2010 (Gomes et al. 2014). This problem is particularly severe in Northern Ontario, which is home to the highest rates of both opioid prescribing and opioid-related death within the province (Gomes et al. 2011).

In a retrospective study on opioid-related deaths in Ontario, 59.5% of deaths involved BZD, a non-opioid central nervous system depressant (Dhalla et al., 2009). The short-term use of BZD is clinically indicated in patients who suffer from anxiety, seizures, or acute alcohol withdrawal. BZD are considered to be high risk for dependence (Nutt et al., 2001), especially when used long-term (Fang et al., 2009). Long-term BZD dependence can cause serious harm including impaired sleep, decreased mood, and a decline in cognitive function (Lintzeris et al. 2010).

BZD are often prescribed to patients who are on opioid agonist therapy (OAT) (Park et al., 2014). In a cross sectional survey of patients in OAT, two thirds of patients reported concurrent BZD use (Nielsen et al., 2007). Another cross-sectional study of 170 OAT patients found that 24% of patients met the criteria for BZD dependence, according to the diagnostic statistical manual of mental disorders-IV (DSM-IV) (Lavie, et al., 2009). The use of BZD during OAT puts patients at an increased risk for overdose and death (Brands et al., 2008). A review of methadone fatalities that involved other drugs found that BZD were detected in 59% of deaths (Mikolaenko et al. 2002). Additionally, patients who are prescribed methadone and use BZD on an ongoing basis are more likely

to continue polydrug use, including cocaine and other opioids (Brands et al., 2008). While previous studies reveal mixed findings about whether ongoing BZD use negatively affects treatment retention, BZD use during treatment has been correlated with a more complex clinical course (Kellogg et al., 2006; Schiff et al., 2007; Brands et al., 2008). Additionally, BZD misuse is correlated with negative patient outcomes such as unemployment, involvement in criminal activity, and psychological distress (Brands et al., 2008).

A review of the literature reveals that most BZD prescribing is in agreement with clinical guidelines, however, there does exist some prescribing that is contrary to clinical guidelines (Adamson et al., 2012). A questionnaire answered by 66 internationally recognized experts on pharmacotherapy suggested that the risks of BZD are over stated and revealed support of long-term BZD use (Uhlenhuth et al., 1999), despite the lack of evidence for effectiveness of long-term BZD use (Nielsen et al. 2015). A qualitative study of 35 general practitioners revealed that physicians are often cautious when initiating BZD use in their patients, however, they view the prescribing of BZD as "the lesser evil" compared to the patient's psychosocial problems (Anthierens et al., 2007).

Along with concurrent drug use, geography is another important factor when studying OAT retention rates. In this study, we focus on differences in BZD use and retention between Northern and Southern Ontario, as well as rural and urban Ontario. An important difference between the North and South is the population density. Northern Ontario has approximately 10% of the population in about 90% of the geographic area. It is for this reason that patients often have to travel large distances to access OAT services and pharmacies to dispense their medication (Eibl et al. 2015). Despite facing a variety of

barriers when accessing care, patients in the North experience increased treatment retention rates (Eibl et al. 2015). Further research must be done to better understand why this occurs, including whether patterns of current drug use, such as BZD, plays a role.

While the potential risks of BZD use during OAT are clear, it is not yet clear whether abstaining from BZD during OAT is beneficial for patients who suffer from co-occurring mental health disorders, where BZD may be clinically indicated. In this study, we evaluate treatment retention for patients using BZD and those who do not; further, we also evaluate whether this is differentially impacted by geographic location.

Methods:

Cohort Definition:

We conducted a retrospective cohort study of patients initiating OAT for the first time between January 1st, 2011 and June 17th, 2012 in the Province of Ontario. We defined first time OAT as no previous history of methadone or buprenorphine use in the network of clinics studied, based on review of records dating back to 1999. Patients started on either methadone or suboxone, which were the only medications approved for opioid dependence in Canada at the time of the study. Patients were allowed to transition between these two medications over the course of treatment. Patients were at least 15 years or older (patients < 18 years of age accounted for < 1% of cohort), and were residents of Ontario. All patients were followed from their date of OAT initiation to the date of drug discontinuation (patient did not receive a methadone or buprenorphine dose for 30 consecutive days), or end of the study period (June 2013).

Data Sources

The dataset used for this study was derived from anonymized electronic medical records from a group of 58 addiction treatment centers across the Province of Ontario – the Ontario Addiction Treatment Centers (OATC). Prior to data analysis, personal identifiers were replaced with an encrypted unique identifier.

BZD Use

Patients were categorized by baseline BZD use (defined as having any BZD positive urine samples in their first month of treatment) and by ongoing BZD use (determined by the proportion of BZD positive urine samples throughout treatment). Urine toxicology screening was performed one to two times per week on all patients throughout their time in care via an enzyme immunoassay, which has the ability to detect BZD in the urine (Handford et al. 2011). However, this test is unable to differentiate between different BZD, which include, but are not limited to: diazepam, clonazepam, and lorazepam. The majority of urine toxicology screens reported were conducted using an antibody reactive to diazepam (and related compounds). Therefore, the use of clonazepam may be underestimated. The detection period and sensitivity differs for each BZD, ranging from a few hours to a few days (Handford et al. 2011).

Definition of Treatment Retention

Unless treatment was terminated, all patients were followed for at least one year to a maximum follow-up date of June 17th, 2013. Continuous OAT was assessed on the basis of not having a period of 30 or more consecutive days without a dose of medication. We defined a patient as having been retained in treatment if they completed at least one year of continuous and uninterrupted OAT. In the event that a patient transitioned to a

non-OATC clinic, was incarcerated, hospitalized, or was otherwise prevented from refilling their prescription, it is possible for type 1 error to occur.

Statistical Analysis

Descriptive statistics were summarized for baseline characteristics of patients, and standardized differences were used to compare patients in the various BZD use groups. Baseline characteristics included: percentage of patients that were male/female, Northern/Southern, and rural/urban, median age, median peak methadone dose, median days retained, the percentage of BZD positive urine samples, and the one-year retention rate. For the purpose of this study, only a patient's first treatment episode was considered. For the primary analysis, a Cox proportional hazard analysis was used to characterize the time to treatment discontinuation and the relative likelihood of treatment termination between the BZD positive and negative patient groups with adjustment for the impact of age, gender, northern and rural location. Cox proportional hazard analysis and log-rank test were performed using SPSS 24. Kaplan-Meier survival analysis was done using GraphPad Prism 7.

Results:

Patient Demographics

Our cohort consisted of 3,850 patients, 60% of which were male with a median age of 31.4 years old. 36% of patients resided in Northern Ontario and 16% lived in a rural setting. Those patients living in the North were 40.7% less likely to drop out of treatment by the one-year mark compared to patients in the South. Male patients were 30.2% more likely to drop out of treatment than female patients. There were no significant differences in treatment retention for patients living in rural or urban centres.

Baseline BZD Use

Patients were stratified by baseline BZD use, which was defined by the presence of any BZD positive urine samples in the first month of treatment. Of the 3,850 patients, 562 (15%) were considered baseline BZD users and 3,288 (85%) non-users. The ratio of female to male patients was greater in the BZD use group with 43.8% of BZD users being female, compared to only 39.9% of non-users being female. Female patients were 34.5% more likely to be baseline BZD users than were males. Another difference in the two groups was in age, with the positive group having an increased median age of 34.3 years compared to 30.8 years. Patients were 25.5% less likely to have a BZD positive urine sample in their first month of treatment if they lived in a rural area and were 23.6% less likely to have a BZD positive urine sample in their first month of treatment if they lived in the North. Baseline BZD users had an increased median peak dose of methadone (85 mg vs. 75 mg) and had a lower median retention of 215 days, compared to 265 days.

Retention and Baseline BZD Use

The following variables were included in the Cox proportional hazard model: age [$_{a}$HR= 0.98 (95% CI 0.975 – 0.984)], gender (female [$_{a}$HR= 0.768 (95% CI 0.70 – 0.84)]), geography (North [$_{a}$HR= 0.59 (95% CI 0.538 – 0.655)] and rural [$_{a}$HR= 0.982 (95% CI 0.863 – 1.118)], and first-month BZD use [$_{a}$HR= 1.149 (95% CI 1.022 – 1.292)]. For those patients considered baseline BZD users, the one-year retention rate was 39.9%. For those patients who were BZD negative on admission, the one-year retention rate was 44%. Of the first month BZD users that remained at one year, 31.2% were BZD positive. Of the baseline non-users who remained at the one-year mark, 95%

were BZD negative. Importantly, patients were 14.9% more likely to drop out of treatment if they had BZD positive urine samples in their first month of treatment.

Proportion of BZD Positive Urine Samples

In addition to being categorized by first-month BZD use, patients were also stratified by the proportion of BZD positive urine samples throughout treatment: 0-25%, 25-50%, 50-75%, and 75-100%. Of the 3,850 patients, 3,556 had BZD positive urine samples less than 25% of the time. These patients experienced a one-year retention rate of 45%. 127 patients had BZD positive urine samples 25-50% of the time, with a retention rate of 32%. These patients were 26.6% more likely to not be retained, compared to those patients in the <25% group. 72 patients had BZD positive urine samples between 50-75% of the time, and they experienced a retention rate of 33%. These patients were 37.4% more likely to terminate treatment prematurely than the <25% group. Lastly, 97 patients had BZD positive urine samples more than 75% of the time, and they suffered the lowest retention rate of 14%. These patients were an alarmingly 174.4% more likely to not be retained in treatment, compared to the <25% group.

BZD Use and Geography

Patients were categorized as residing in Northern Ontario or Southern Ontario according to the Local Health Integration Network (LHIN) in which they lived; patients residing in LHIN 13 or 14 were considered Northern residents. For the proportion of BZD positive urine samples, patients in the North had retention rates of 56%, 33%, 17%, and 13%, respectively. Patients in the South experienced retention rates of 38%, 32%, 36%, and 14%. In the Northern population, the greater the proportion of BZD positive urine samples, the lower the retention. However, in the Southern population, the decrease

is less pronounced. Instead, it appears that patients with >75% of urines BZD positive suffer the lowest retention rates.

Discussion:

Previous studies have revealed mixed findings about whether BZD use impacts OAT retention. A review of BZD use in OAT suggests that most studies have found that baseline BZD use is not predictive of decreased retention (Lintzeris et al. 2010). However, this is contrary to our findings. Our findings support the idea that baseline BZD use is predictive of treatment drop out, with these patients being 14.9% more likely to terminate treatment prematurely. Additionally, our results indicate that with increasing proportion of BZD positive urine samples, patients are at increased risk of premature dropout. Therefore, both BZD use at treatment outset and intensity of BZD use during OAT are correlated with decreased retention.

Compared to previous studies on patients in OAT, the median age of our patient sample was younger, at 31 years (median age = 34.6 Brands et al. 2008; median age = 35 Lavie et al. 2009; median age = 47 Chen et al. 2011). However the age distribution in our OAT treatment data set seems to reflect the opioid dependent population in Ontario at the time of the study. This is supported by a cross-sectional study of all opioid-related deaths in Ontario between 1991 and 2010, which found that most opioid-related deaths occurred among young adults aged 25-34 (Gomes et al. 2014). A study relying on self-reports of high schools students found that opioid use is increasing among adolescence (McCabe et al. 2012), therefore, it is possible that the opioid dependent population in Ontario has gotten younger in recent years, compared to the times and locations at which the other studies on BZD were conducted.

In terms of concurrent drug use, 15% of our patient population was BZD positive in their first month of treatment. Compared to previous studies, this number is low (Lintzeris et al., 2010). Our findings indicate that BZD use is more prevalent in the female population, which is supported by previous studies (Brands et al., 2008). The increased use of BZD in this population may be explained by the fact that females in OAT suffer from more psychiatric comorbidity than their male counterparts (Rowan-Szal et al., 2000; Peles et al., 2007). Studies have also found that female patients are more likely to receive a BZD prescription than are males (Bramness et al. 2007) and that the risks associated with BZD prescribing (ie. hospital visits, accidental injury) are increased in the female population (Schuman-Olivier et al. 2013). We also found a difference in the age of baseline users and non-users, with baseline users having a median age of 34.3 years and non-users having a median age of 30.8 years. It may be the case that patients who have more severe mental health disorders (and therefore use BZD) take longer to come to treatment.

Our results suggest that geography is an important factor to consider when studying BZD use. We found that patients living in rural areas and those patients living in the North were less likely to be baseline BZD users. When studying the impact of geography on retention, we confirmed the earlier finding that patients in the North were more likely to be retained in treatment, however we failed to confirm in this smaller sample size the correlation between rurality and retention (Eibl et al. 2015). The increased retention in the North may seem surprising, given that these patients face a variety of barriers when accessing health care. In remote Northern communities, patients often have to travel long distances to access OAT prescribing physicians and the

pharmacy that dispenses their methadone or buprenorphine (Eibl et al. 2015). It seems somewhat intuitive that given the added difficulties, these patients would experience decreased retention. However, this is not the case. In fact, patients in the North were 41% less likely to terminate treatment prematurely than were Southern patients. Given that Northern patients are less likely to be BZD users and BZD use is predictive of dropout, the increased retention may be partially explained by less BZD use in the North. However, given that this population was more likely to use cocaine and that cocaine use is predictive of treatment dropout, there are likely other reasons why this population benefits from greater retention. The enhanced treatment retention may be explained by Northern patients who overcome the barriers to treatment entry being more motivated to be successful in their treatment. The decreased BZD use in Northern and rural patients may be explained by inaccessibility in terms of availability or cost of non-prescribed BZD.

Of the 3,288 patients who were considered baseline non-users, the vast majority (~95%) who were retained were also BZD negative at the one year mark. For the remaining 5%, it may be the case that patients received a BZD prescription during the course of their treatment. Of the 562 patients who were BZD positive in their first month of treatment, 49% of those that were retained were negative at 3 months, 59% at 6 months, 61% at 9 months, and 69% at the one-year mark. Given that OAT does not treat BZD dependence, it may seem surprising that the majority of BZD users terminate BZD use during treatment. However, it may be the case that many of the initially positive patients were heavy BZD users and dropped out of treatment before reaching the 3rd, 9th, or 12th month. It may also be the result of contingency management, whereby a patient is

motivated to abstain from concurrent drug use in order to obtain carried (i.e. take home) doses. Contingency management might encourage a patient to decrease BZD use, given that it has been shown to reduce the use of other drugs in patients who are receiving OAT (Rawson et al. 2002).

Although our patient sample had fewer BZD users than expected, it is important to consider why BZD use is so prevalent in OAT. One theory is that there is an increased prevalence of co-morbid mental health issues including depression, anxiety, and insomnia among patients enrolled in OAT (Carpentier et al., 2009; Mark et al., 2013). It is for this reason that patients are often prescribed BZD to treat their concurrent mental health disorders (Jones et al., 2012). A retrospective cohort study of over 2,000 patients receiving OAT found that 40% of patients had received at least one BZD prescription (Bramness et al., 2007). The current guidelines on how to manage patients with opioid dependence and co-occurring mental health disorders, for which BZD are clinically indicated, are unclear (CPSO 2011). Further research needs to inform physicians as to how they should manage these complex patients. However, not all BZD use is prescribed. A retrospective study of patients receiving methadone found that nearly 35% of patients who were BZD positive did not have an associated prescription (White et al. 2014).

One of the main limitations of this study is the inability to detect whether a patient received a BZD prescription from a physician other than their OAT provider. The number of patients that received a BZD prescription from their OAT provider was known, however, this number was less than 7.2%. This is likely because the majority of BZD prescriptions are coming from physicians outside the OATC network. A retrospective cohort study that utilized a prescription database found that over 60% of BZD

prescriptions were written by a physician other than the OAT provider (Bramness et al. 2007). Therefore, it is very likely that our detection of BZD prescriptions is insufficient. While this study captures the impact of general BZD use on OAT retention, it does not necessarily differentiate between clinical BZD use for mental health disorders, and non-prescribed use. It is possible that a large proportion of our patient sample did have BZD prescriptions and were using BZD as clinically prescribed from a non-OAT physician. Another limitation is that we were unable to determine the dose of BZD taken by patients. Lastly, if a patient dropped out of treatment, we were not able to determine whether the patient simply terminated all OAT, began treatment at a non-OATC clinic, was incarcerated, hospitalized, or died.

This study also has several strengths. While BZD use in OAT has been studied previously, it has not been studied in a regional context – in this case Northern vs. Southern Ontario. Of the studies that have been done, few have been longitudinal. Those studies that were longitudinal either had a much smaller sample size, relied on self-reported data, or did not use a survival analysis to quantify the impact of BZD use and geography on treatment retention. Other strengths regarding study design include the large sample, the method of data collection, and the patient population. With nearly 4,000 patients in our cohort, this study captures a substantial proportion of all patients receiving OAT in Ontario. Additionally, this study did not rely on patient self-report, as did many of the previous studies. Lastly, the fact that all patients in the cohort were from one network of clinics adds strength to the comparisons made between patients.

The findings of this study suggest that BZD use is a marker for greater clinical complexity, and puts patients at increased risk of premature OAT discontinuation. Given

that treatment retention is correlated with better patient outcomes (Peles et al. 2008; Nosyk et al. 2010), it is important that physicians be cognizant of BZD detection in patients' urine samples, as this could be a marker for decreased retention. Physicians should exercise caution when prescribing BZD to patients on OAT. However, further research needs to be done to better understand how prescribed BZD use and non-prescribed use differentially impact treatment retention.

Table 2. Characteristics of baseline BZD users and non-users. Descriptive statistics were summarized for baseline characteristics of patients, and standardized differences were used to compare patient groups. Patients were considered baseline BZD users if they had any BZD positive urine samples in the first month of treatment.

		Initially Negative (n = 3288, 85.4%)	**Initially Positive (n = 562, 14.6%)**
Male / Female		1975 (60.1%) / 1313 (39.9%)	316 (56.2%) / 246 (43.8%)
North / South		1239 (37.7%) / 2048 (62.3%)	166 (29.5%) / 396 (70.5%)
Urban / Rural		2753 (83.8%) / 543 (16.2%)	499 (88.8%) / 63 (11.2%)
Median Age (Q_1, Q_3; SD)		30.8 (25.3, 39.4; SD=10.2)	34.3 (28.1, 45.3; SD=10.9)
Median Peak Methadone Dose (Q_1, Q_3; SD)		75 (50, 100; SD=33)	85 (55, 115; SD=36)
Median Peak Suboxone Dose (Q_1, Q_3; SD)		8 (8, 16; SD=7)	12 (8, 20; SD=8)
Median Days Retained (Q_1, Q_3; SD)		265 (56, 526; SD=272)	215 (53, 519; SD=270)
Median Percent Positive Results (Q_1, Q_3; SD)		0.0 (0.0, 0.0; SD=4.9)	21.4 (6.8, 55.1; SD=32.1)
Percent Positive Results	[0, 25)	3252 (98.9%)	302 (53.7%)
	[25, 50)	31 (0.9%)	96 (17.1%)
	[50, 75)	4 (0.1%)	68 (12.1%)
	[75, 100]	1 (<0.1%)	96 (17.1%)
At Month 3 Day 60 to 90	Positive / Negative	144 (6.0%) / 2276 (94.0%)	204 (50.5%) / 200 (49.5%)
	Retained	2420 (73.6%)	404 (71.9%)
At Month 6 Day 150 to 180	Positive / Negative	109 (5.6%) / 1850 (94.4%)	128 (40.9%) / 185 (59.1%)
	Retained	1959 (59.6%)	313 (55.7%)
At Month 9 Day 240 to 270	Positive / Negative	88 (5.2%) / 1601 (94.8%)	104 (39.0%) / 163 (61.0%)
	Retained	1689 (51.4%)	267 (47.5%)
At Month 12 Day 330 to 360	Positive / Negative	80 (5.3%) / 1443 (94.7%)	74 (31.2%) / 163 (68.8%)
	Retained	1523 (46.3%)	237 (42.2%)
Retained / Not-Retained 365 Days		1447 (44.0%) / 1841 (56.0%)	224 (39.9%) / 338 (60.1%)

Figure 2.1 - Treatment retention by baseline BZD use. A cox proportional hazard analysis was used to characterize the time to treatment discontinuation between the patient groups. Log-rank comparison of these curves yielded a Chi-Square value of 2.883 with a non-significant p value of 0.0895. Baseline BZD users were 14.9% more likely to drop out of treatment than baseline non-users [$_{a}$HR=1.15(95% CI 1.02 –1.29)].

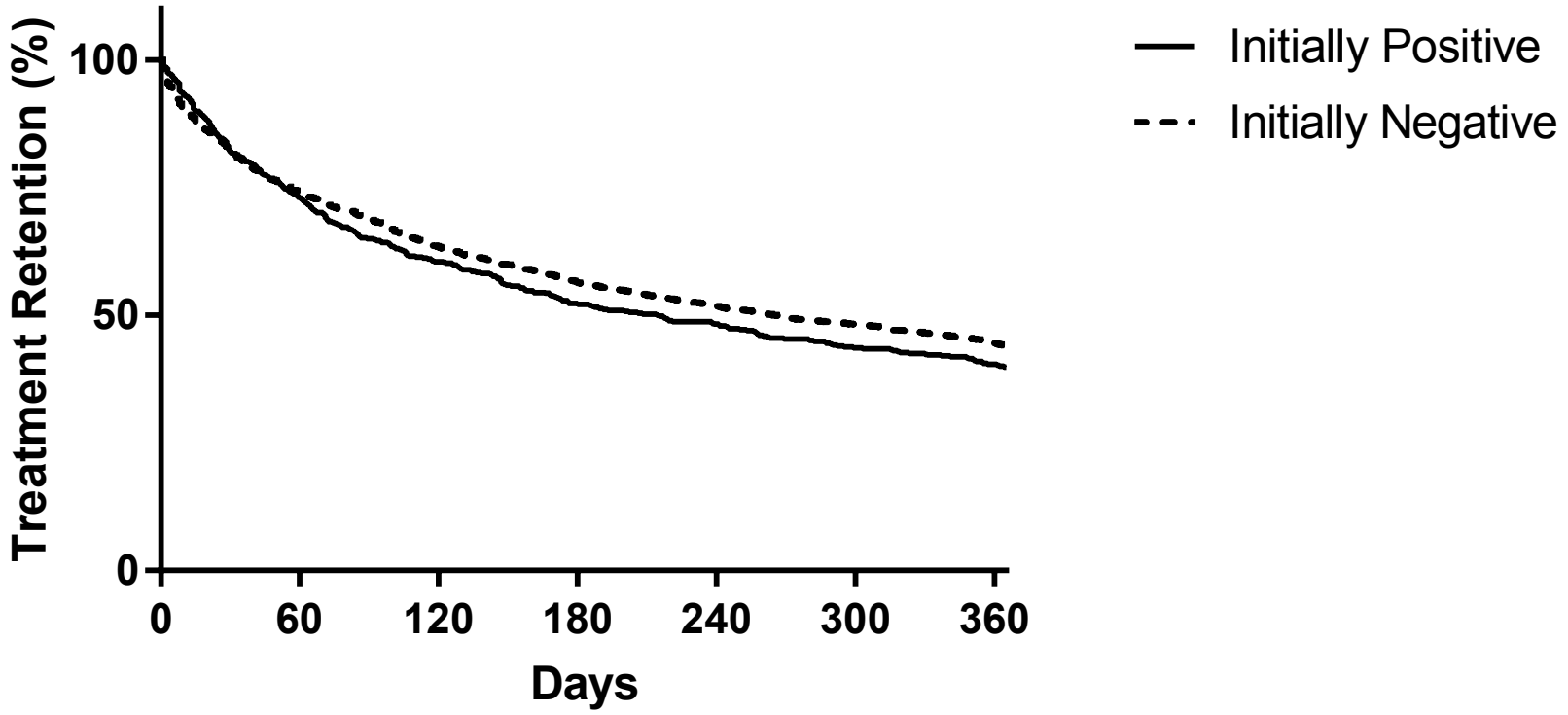


Figure 2.2 - Treatment retention by proportion of BZD positive urine samples. A cox proportional hazard analysis was used to characterize the time to treatment discontinuation across the four patient groups. Patients with 25-50% of urines BZD positive were 26.6% more likely to drop out of treatment than patients in the 0-25% reference group [$_{a}$HR=1.26 (95% CI 1.02 –1.57)]. Patients with 50-75% of urines BZD positive were 37.4% more likely to drop out of treatment than patients in the 0-25% reference group [$_{a}$HR=1.37(95% CI 1.03 –1.832)]. Patients with 75-100% of urines BZD positive were 174.4% more likely to drop out of treatment than patients in the 0-25% reference group [$_{a}$HR=2.74(95% CI 2.19 –3.43)]

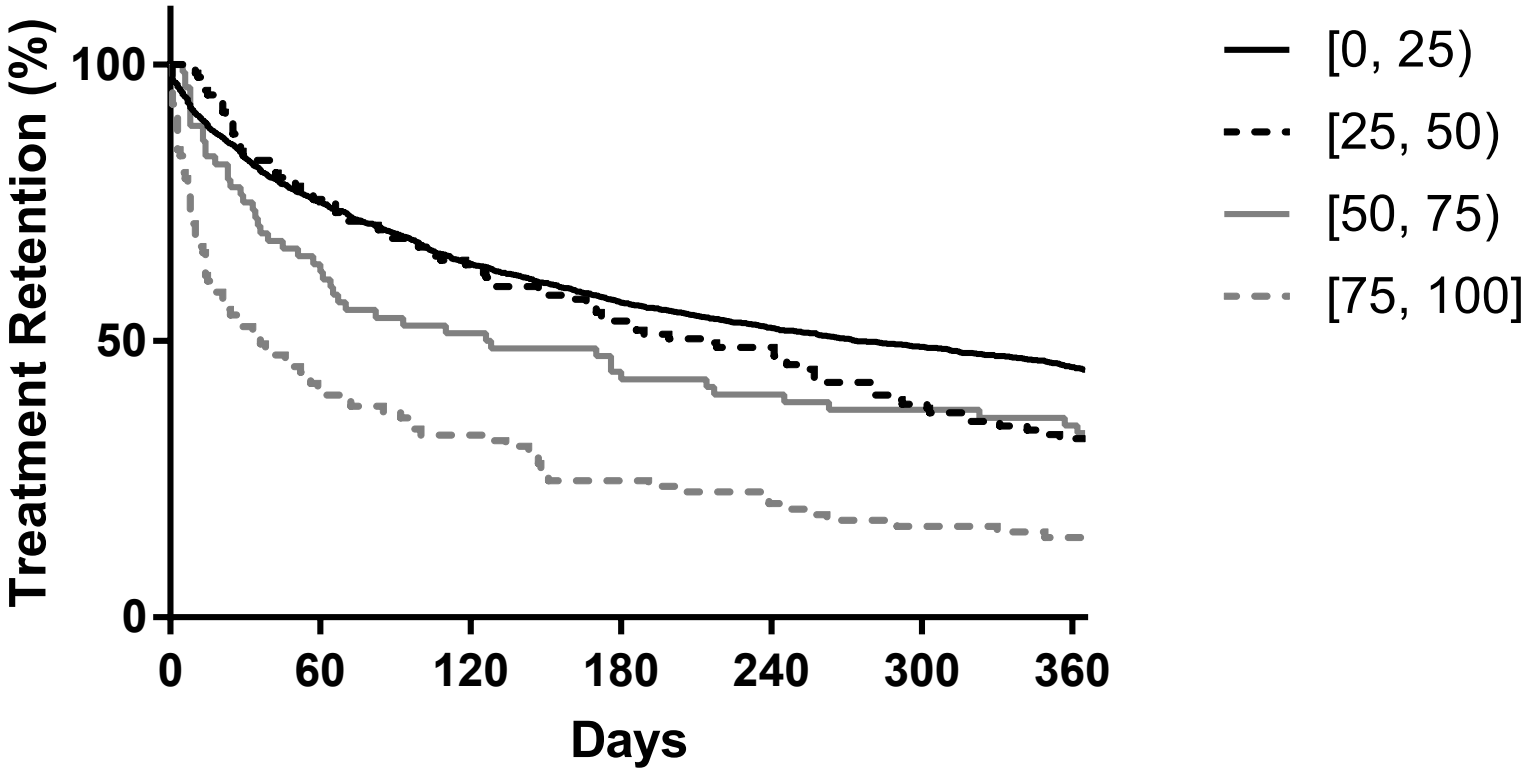
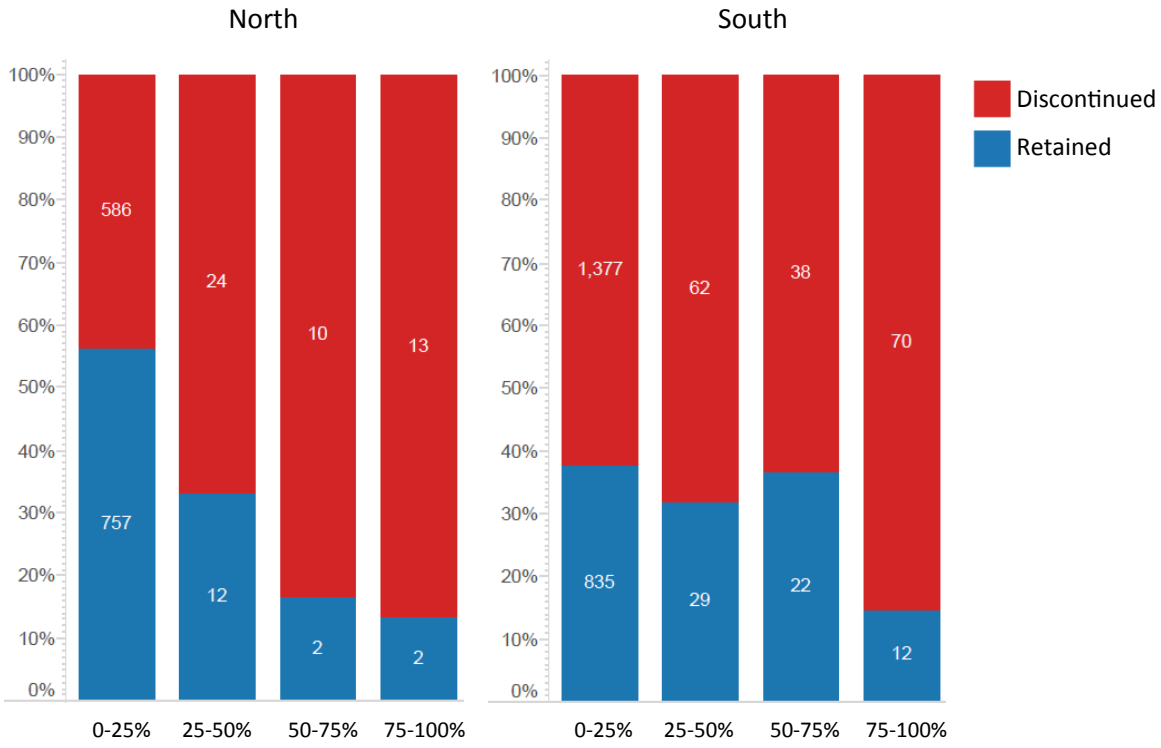


Figure 2.3 - Proportion of patients retained in treatment for one year, by frequency of BZD use, comparing North vs. South. The pattern of decreased retention with increased proportion of BZD positive urine samples is not seen in the Southern population, as it is in the Northern population. However, Southern patients with a high proportion of BZD positive urine samples (≥75%) experienced decreased retention rates. Cross tabulations were performed and a signification association was found with the first (0-25%) group (Chi-Square value = 117.1, p = 0.000), but not with the other groups (p>0.05).



Chapter 4: Conclusion

Opioid Dependence

The prevalence of opioid dependence in Canada is on the rise (Green et al. 2011), which has serious implications for both opioid dependent individuals and society at large. The annual social cost of untreated opioid dependence in Canada is estimated to be over $45,000 dollars per user (Wall et al. 2000). This is in large part due to crime, law enforcement, utilization of health care services, and loss of productivity (Wall et al. 2000). Along with an increase in the prevalence of opioid dependence, the rate of opioid prescribing in Ontario has risen substantially in recent years (Dhalla et al. 2009). With the addition of oxycodone to the Provincial drug formulary in 2000, oxycodone prescribing increased by 850% between 1991 and 2007 (Dhalla et al. 2009). This increase in opioid prescribing was associated with a 41% increase in opioid related death (Dhalla et al. 2009), which rose 242% the following 20 years after 1991 (Gomes et al. 2014).

Treatment Options

Opioid agonist therapy (OAT) is the most effective form of treatment available to those patients who have developed opioid dependence. OAT is a substitution therapy whereby the patient is relieved of their opioid withdrawal, thereby eliminating the need to use opioids illicitly. Methadone and buprenorphine/naloxone (Suboxone) are the two most frequently used medications to treat opioid dependence in Canada. Methadone is a long acting opioid that is a full agonist, compared to buprenorphine, which is a partial agonist (CPSO 2011), Physicians require a special license to prescribe methadone (CPSO 2011), which increases barriers for patients trying to access it. This is particularly true of remote Northern communities, where methadone is often unavailable (Kiepek et al.

2012). Suboxone has fewer prescribing limitations, but is not widely available in Canada due to restricted coverage in Provincial formularies, which changed significantly in Ontario in 2012. Other treatment options that are not available in Canada are slow-release morphine and intramuscular slow-release naltrexone, both of which have been shown to be effective in the treatment of opioid dependence (Winklbaur et al. 2008; Nunes et al. 2015).

OAT is a form of maintenance therapy, rather than a detoxification. Research has found that a maintenance-oriented approach to treating opioid dependence is more effective in reducing illicit opioid use and in retaining patients than is a detoxification approach (Woody et al. 2008). Studies have also found that gradual dose decreases mixed with dose stabilization is more effective in achieving long-term abstinence compared to tapering the methadone dose to zero (Nosyk et al. 2012).

Benefits of OAT

The benefits of OAT are widespread. OAT has been shown to reduce harm and allow patients to return to normal social, psychological, and physical functioning (Health Canada 2002). In addition to reducing illicit opioid use, OAT has also been shown to reduce concurrent drug use, including the use of cocaine and sedatives (Mattick et al. 2014). OAT is also effective in reducing criminal activity, the risk of communicable disease, and mortality (Brands et al. 2002). Studies have found an immediate increase in the health-related quality of life in those patients who initiate OAT (Nosyk et al. 2015), as well as improved pregnancy outcomes for pregnant opioid-dependent women (Brands et al. 2002). However, the positive effects of OAT are maximized when patients are retained in treatment for at least one full year. When this occurs, patients experience a

variety of positive health outcomes including reduced drug use, relapse, hospitalization, and mortality (Peles et al. 2008; Nosyk et al. 2010). In addition to providing a variety of health benefits, both methadone and buprenorphine are substantially less costly than no treatment at all (Connock et al. 2007).

OAT in Ontario

The availability of OAT has increased substantially in recent years with more than 42,000 patients currently receiving OAT in Ontario (CPSO, 2015). Despite this, certain areas of the province – such as Northern rural communities – do not have access to these services (Kiepek et al. 2012). Northern Ontario has a chronic shortage of health care services (Strasser et al. 2008), a vast geographic landscape (Strasser et al. 2008), and a high prevalence of opioid use and opioid related death (Gomes et al. 2011) and many patients struggle to access this form of treatment.

Despite the barriers that people living in Northern communities face, it was previously found that Northern Ontario patients experience better OAT retention than Southern patients (Eibl et al. 2015). The results of this thesis corroborate these findings, and may help explain why this pattern exists. It was previously postulated that the increased retention in the North may be due to less cocaine use. However, we found that cocaine use was more prevalent in the North than in the South. Therefore, the increased retention experienced by this group of patients is not because of less cocaine use. Instead, our findings strengthen the hypothesis that patients in the North who overcome the barriers in accessing OAT are more motivated to be successful in treatment. However, there does exist the possibility that the increased retention rates are due in part to less BZD use, as Northern patients were less likely to be baseline BZD users than were

patients in the South. However the magnitude of the impact of lower BZD use is insufficient to fully explain the geographic differences in outcome. We found that patients residing in rural communities used less cocaine and less BZD than patients in urban settings. As mentioned previously, we found that Northern patients were more likely to use cocaine, but less likely to use BZD than their Southern counterparts. Further research needs to be done to understand whether this is a result of drug accessibility, or a result of BZD prescribing practices.

Impact of Cocaine on OAT

While OAT has been found to provide a variety of positive health benefits for patients, the course of treatment may be negatively impacted by concurrent drug use, such as the use of cocaine. Cocaine is a stimulant that causes dopamine accumulation at the brains synapse, leading to an increase in alertness (NIDA 2010). The existing literature on cocaine use in OAT is rather conclusive that cocaine use is correlated with decreased retention (DeMaria et al. 2000; Downey et al. 2000; Hartel et al. 1995; Magura et al. 2002; Brands et al. 2008; Salamina et al. 2010,;Sullivan et al. 2010, Proctor et al. 2015). In this thesis, we found that this is true of both baseline and ongoing cocaine use. In addition to being at increased risk of drop-out, patients who use cocaine while receiving OAT have an increased risk profile for HIV (Grella et al. 1995), require increased doses of methadone (Maremanni et al. 2000), are more likely to use illicit opioids (Hartel et al. 1995), are more likely to suffer from psychological distress (Roux et al. 2016), and are at an increased risk of overdose (Visconti et al. 2015). Therefore, in addition to being correlated with decreased retention, the literature is conclusive that cocaine use in OAT is associated with poorer health outcomes for patients in general.

Impact of BZD on OAT

Unlike with cocaine, the literature on BZD use and OAT retention is rather inconclusive. BZD are a class of psychoactive drugs that are non-opioid central nervous system depressants. BZD are typically used to treat anxiety, seizures, and acute alcohol withdrawal (Brands et al. 2000; Canadian Agency for Drugs and Technologies in Health, 2014). BZD are clinically indicated for short-term use, and there exists little evidence to support its long-term use. Additionally, the use of BZD while in OAT puts patients at an increased risk of overdose and death, with as many as 32-50% of methadone or buprenorphine-related deaths involving BZD (Chan et al., 2006; Mikolaenko et al. 2002; Schifano et al., 2005; Shah et al., 2005). Studies have found that BZD use does not impact treatment retention (Kellogg et al., 2006; Peles et al. 2006; Brands et al. 2008), and others have found that it is predictive of premature drop-out (Schiff et al. 2007; Peles et al. 2010; Specka et al. 2011). Of note, members of our research group previously conducted a retrospective chart view of 172 patients receiving MMT in Toronto and found that ongoing BZD use was not correlated with decrease retention rates (Brands et al. 2008). However, this study was not able to differentiate between prescribed and non-prescribed BZD use. Additionally, studies have found that baseline BZD use is correlated with lower retention rates, but that ongoing use is not (Eiroa-Orosa et al. 2010). This study includes a much larger sample size than previous studies on BZD use, determines BZD use through toxicology testing and clearly demonstrates that BZD use is correlated with decreased retention in OAT.

Due to the conflicting literature, there currently exists a gap in knowledge with respect to how to manage patients who are clinically indicated for BZD, and are also

receiving OAT. More research needs to be done to better understand the role that concurrent BZD use plays on OAT outcomes, including whether prescribed vs. non-prescribed BZD use differentially impacts treatment retention.

Several studies have investigated the predictors of BZD use in OAT. Studies have found that being female (Brands et al., 2008), being Caucasian (Chen et al., 2011), having a history of psychiatric comorbidity (Brands et al., 2008, Chen et al., 2011), early onset of opioid use (Backmund et al., 2005), unemployment (Backmund et al., 2005, Bleich et al., 2002), having a previous history of imprisonment (Backmund et al., 2005, Bleich et al., 2002), and a history suicide attempts (Backmund et al., 2005) are associated with a greater likelihood of BZD use. Of note, an Isreali group found that males were more likely to be BZD abusers (Bleich et al., 2002). Additionally, a Norwegian study that examined BZD prescriptions found that females were more likely to be prescribed BZD than were males (Bramness et al., 2007). The results of this thesis found that female patients were 35% more likely to be BZD users than male patients and that BZD use was predictive of decreased retention.

Impact of Treatment Program Characteristics

While patient characteristics – such as concurrent drug use – may be of great importance in determining the outcome of OAT, treatment characteristics play an important role as well (Ball and Ross 1991). Certain OAT programs have been found to have much higher retention rates, which may be attributable to characteristics of the treatment program themselves, rather than patient characteristics (Ball and Ross 1991). In one retrospective study of patients receiving OAT at the Centre for Addiction and Mental Health in Toronto, the treatment program consisted of physicians, nurses, and therapists

(Brands et al. 2008). In this treatment program, patients received much more holistic care in treating their opioid dependence than is typically experienced and patients benefited from a two year retention rate of 60% (Brands et al. 2008). Therefore, the lower one-year retention rate of 43% may speak to the need for more holistic care in the OAT model. Particularly, patients who are deemed high risk of drop out (ie. BZD and cocaine using patients) may benefit from have programs with sufficient resources to address all of their treatment needs.

Cannabis Use in the Opioid Dependent

While it is clear that concurrent drug use – in the form of cocaine and BZD use – may compromise the OAT clinical course, it may be the case that some concurrent drug actually correlates with more positive patient outcomes. Both Canada and the US have modified their laws with respect to medical cannabinoid use given its therapeutic role (Benyamina et al. 2014), and this appears to have had a positive effect on the opioid dependent population. A retrospective study of opioid overdose deaths from 1991 to 2010 in the US found that the opioid overdose mortality rate per 100,000 population was 25% lower in those states with medical cannabis laws (Bachhuber et al. 2015). A separate study found that patients receiving opioid medication for chronic pain greatly benefit from medical cannabis use in terms of reduced opioid use. This retrospective cross-sectional study found that patients using cannabis for chronic pain experienced 64% less opioid use, increased quality of life, and benefited from fewer side effects (Boehnke et al. 2016). While this thesis did not study the role of cannabis in OAT, this is something that requires further study as cannabis use may be correlated with enhanced patient outcomes.

Dataset

The dataset used for this thesis was derived from anonymized electronic medical records from a network of 58 clinics across the Province, the OATC. This dataset includes patient demographics (age, gender, geographic location) as well as the results of patient urine toxicology results. Urine toxicology screening is typically done once or twice per week for all patients in this network of clinics. The results of urine toxicology screening dates back to 1999, with appointments dating back to 2004.

Analysis

The time frame of this study was chosen as January 1st 2011 to June 17th, 2012, despite the fact that we had urine toxicology results dating back to 1999. The reason this study window was chosen was because of missing methadone dose dates in the year 2010, therefore, patients would have been incorrectly captured as having terminated treatment, or potentially incorrectly captured as being a first-time patient. Only patients who were initiating first-time OAT were considered. Therefore, patients were excluded if they had previously initiated OAT in this clinic network (dating back to 1999). Patients were considered as being retained in treatment if they did not go a period of time of 30 days without receiving a prescription for methadone or suboxone. This time period was chosen in order to capture a patient's first treatment episode. The intention was to quantify a time from the day they initiate treatment to the day they leave treatment, while giving patients enough flexibility to miss an appointment or have a brief period of hospitalization or incarceration (during which OAT is typically continued in Ontario).

Findings

Both baseline and ongoing drug use was predictive of decreased retention. This was true of both cocaine and BZD. The higher the proportion of cocaine or BZD positive urine samples, the more likely patients are to terminate treatment prematurely. Similar to previous studies (Eibl et al. 2015), it was found that patients in the North are retained at a higher rate than patients in the South. Patients in Northern Ontario were less likely to use BZD, but more likely to use cocaine than patients in the South. Patients in rural communities were less likely to use cocaine and BZD than were their urban counterparts. With respect to both cocaine and BZD, concurrent drug use decreased with treatment duration. For the most part, these findings are in agreement with the existing literature.

Limitations

One of the main considerations that requires more study is the difference in prescribed and non-prescribed BZD use, which was not done in this thesis. To better understand the impact of clinical BZD use on OAT retention, further research must be done using prescription data, such as data from the Institute for Clinical and Evaluative Sciences (ICES). Linking datasets from ICES with the OATC urine toxicology screening could allow for the identification of those patients who have received a BZD prescription and are using BZD as clinically indicated, and compare their retention to patients using non-prescribed BZD (those without a prescription but who have BZD positive urine screens). Differentiating between the two would better inform physicians as to how to manage patients who are in OAT and are also clinically indicated for BZD. This would also potentially allow us to study drug diversion by identifying those patients who fill a BZD prescription but do not have BZD positive urine samples.

Other limitations of this thesis include a potential for selection bias, potential lack of external validity, the inability to determine certain patient details, and the limitations surrounding the type of urine toxicology screening used. The potential for selection bias lies in the fact that only one network of clinics offering OAT was studied. This is the largest network of OAT providing clinics in the province and consists of a substantial number of patients receiving OAT in Ontario, however, the results of this thesis may not be generalizable to all patients receiving OAT in Ontario, Canada, or worldwide. Due to the retrospective nature of our research, we were unable to determine certain patient details that were not included in the dataset. Details such as years of drug use, or the amount of drug taken remain unknown. Additionally, if a patient terminated treatment we were unable to determine whether they terminated all OAT, switched to a different network of clinics, had an extended hospital stay or incarceration, or died. If it was the case that a patient died, this would be considered a negative outcome and this patient would be captured in our definition of not retained. However, if a patient transitioned to a non-OATC clinic, this would be a positive outcome that would also be captured in our definition of not retained, which in this case, would be a misidentified negative outcome. Lastly, the urine toxicology screening used is an immunoassay that does not use confirmatory quantitative testing such as gas chromatography or mass spectrometry. Therefore, there is the potential for false positive or false negative results. However the products used during the time of this study were approved by Health Canada and meet high clinical standards for sensitivity and specificity.

Importantly, the framework used in this research (the transtheoretical model) has its own limitations. Unlike other frameworks that describe health behaviour, the

transtheoretical model does not utilize a continuum, but rather distinct categories: pre-contemplation, contemplation, preparation, action, or maintenance. Therefore, patients can only be classified as being in one of five discrete stages, which may not accurately describe each individual patient. Additionally, because of the retrospective nature of our research, we aren't able to determine where patients were likely to be categorized within the stages of change. Secondly, the time frames that characterize each category are arbitrary and inflexible. For example, if a patient intends on modifying their health behaviour within the next three weeks, they are considered to be in the preparation stage. However, if they plan on modifying their health behaviour within the next five weeks, they remain in the contemplation category. Thirdly, there is no objective focus on the patient's actual preparedness for change with this model. Instead, the categorization relies entirely on the patient's self-reported intention to quit. While this is certainly important to consider, their intention to change their health behaviour may be unrealistic or unreliable. Lastly, this model does not consider the uniqueness of certain populations (age, gender, race, geographic residence) and therefore may not apply to all demographics equally.

Implications for Further Research

The findings from our research have implications to inform clinical guidelines and physician practice. It is clear from our findings that baseline BZD and cocaine use are markers for premature drop-out, and that the higher the incidence of concurrent drug use, the more likely patients are to drop-out. Physicians should be aware of BZD and cocaine detection in urine toxicology screening, and these patients should be closely monitored throughout treatment. With further research regarding prescribed BZD use and OAT retention, we could inform physicians as to whether BZD should be prescribed to

patients in OAT. As it stands, physicians should be cautious when prescribing BZD to these patients, as this may put patients at increased risk of premature drop-out, overdose, and death. For patients with cocaine use, particularly when it is high intensity and sustained, the risk of premature dropout is markedly higher and physicians should consider adding additional treatment modalities early in care.

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Appendix

Ethics Review

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